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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of:

Connie Sánchez et al. Confirmation No.: 7268

Application No.: 10/021,126 Art Unit: 1614

Filed: December 12, 2001 Examiner: F. Krass

For: Treatment of Neurotic Disorders

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Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

**DECLARATION OF CONNIE SÅNCHEZ**

I , Connie Sånchez, do hereby declare and state as follows:

1. I am a citizen of Denmark and more than 21 years of age.

2. I am a co-inventor of the subject matter described and claimed in the above-identified patent application.

3. I am the author of the article *Eur J. Pharm.*, 465:155-158 (2003), "R-Citalopram Attenuates Anixolytic Effects of Escitalopram in a Rat Ultrasonic Vocalisation Model".

4. At page 157 (right column, second full paragraph), the article refers to an experiment involving isolated guinea pig ileum. The procedure and results for that experiment are provided below.

5. The ability of R-citalopram to act as a histamine $H_1$ receptor antagonist was evaluated by determining its ability to inhibit histamine induced contraction of guinea pig ileum in vitro. The experimental protocol, which was adapted from Christensen et al., *Eur. J. Pharm.* 41:153-162 (1977), Christensen et al., *Life Sci.* 34:1529-1540 (1984), Hyettel et al., *J. Neurochem.* 44:1615-1622 (1985), and Svendsen, et al. *Drug Dev. Res.* 7:35-47 (1986), is as follows. 400-600 g Guinea pigs of either sex were used.

6. The caudal part (about 15 cm) of an ileum was removed from guinea pigs (400-600 g) and cleaned in Tyrode solution at 20° C. The Tyrode solution (NaCl 137 mM, KCl 2.7 mM, $CaCl_2$ 1.8 mM, $MgCl_2$ 1.1 mM, $NaH_2PO_4$ 0.32 mM, $NaHCO_3$ 4.8 mM, glucose 5.0 mM) was saturated with $O_2$.

7. Individual ileum samples were prepared by cutting the ilieum into pieces (2.5-3.0 cm in length) followed by suspension in 10 ml organ baths containing Tyrode solution at 37° C, gassed continuously with $O_2$.

8. Each sample was loaded with a 1 g weight and a Grass TF 03 transducer (Grass-Telefactor, West Warwick, RI) was attached to record isotonic measurements. Contractions were induced by the addition of 1100 mM histamine followed by washing after 30 seconds. Once 3 or 4 equal contractions were observed the test drug was added to the bath and after 3 minutes contractions were induced by the addition of 1100 mM histamine.

9. At least five concentrations of the drug were evaluated for its ability to inhibit histimine induced contractions. Inhibition was expressed as the percent difference between the first contraction following addition of the drug and the mean of the two contractions prior to addition of the drug.

10. The $IC_{50}$ for R-citalopram as determined by this procedure was 2700 mM.

11. The tabulated results of a footshock-induced ultrasonic vocalization experiment in adult rats are shown in Table 1 on page 156 of the 2003 *Eur J. Pharm.* article. The experiment was performed as described in section 2.2 on pages 156 and 157 of the article.

12. The complete results for the footshock-induced ultrasonic vocalization experiment are shown below.

| Drug | Dose (mg/kg) | Response (sec) | S.E.M. |
|---|---|---|---|
| Citalopram | 0 | 116.66 | 10.45 |
| | 0.13 | 89.25 | 27.54 |
| | 0.25 | 69.52 | 16.05 |
| | 0.5 | 41.74 | 7.50 |
| | 1.0 | 69.71 | 13.85 |
| | 2.0 | 63.84 | 10.50 |
| | 4.0 | 82.50 | 24.96 |
| Escitalopram | 0 | 87.50 | 17.00 |
| | 0.24 | 71.40 | 17.00 |
| | 0.49 | 40.60 | 24.00 |
| | 1.0 | 20.90 | 11.00 |
| | 3.9 | 6.60 | 4.20 |
| Citalopram + l-5-HTP | 0 | 116.66 | 10.45 |
| | 0+l-5-HTP | 95.50 | 14.00 |
| | 0.064 | 109.30 | 21,50 |
| | 0.25 | 116.00 | 19.50 |
| | 0.50 | 54.00 | 15.,70 |
| | 1.0 | 54.70 | 13.70 |
| | 2.0 | 29.60 | 13.70 |
| | 4.0 | 36.40 | 11.00 |
| | 8.0 | 0 | 0 |
| Escitalopram+l-5-HTP | 0 | 87.50 | 17.00 |
| | 0+l-5-HTP | 102.00 | 26.80 |
| | 0.031 | 69.60 | 31.00 |
| | 0.063 | 56.00 | 22.20 |
| | 0.13 | 1,86 | 8.10 |
| | 0.24 | 6.70 | 6.73 |

13. I further declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true. I further declare that these statements are made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under

1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the instant application or any patent issued thereupon.

Connie Sánchez

Date 2/9/2005

Connie Sánchez